**WHAT IS SKIN?**

Skin is the body’s largest organ. It regulates temperature, protects against germs, and allows for the sense of touch. Skin is made up of three layers:

- **The epidermis** is the outer layer of skin, providing protection and generating new skin cells. It consists primarily of three types of cells: squamous cells, basal cells, and melanocytes.
  
  Basal cells form the bottom of the epidermis and are constantly dividing to create new cells. As skin sheds, the new cells move toward the surface. As they reach the surface, they flatten out and become squamous cells.

  Melanocytes are the cells that create melanin, the substance that gives skin its color.

- **The dermis** is the inner layer of skin, containing collagen for elasticity, nerve endings for touch, and housing hair follicles, oil glands, and sweat glands.

- **The subcutis** is the deep layer of fat that cushions muscles and bones, regulates temperature, and houses nerves and blood vessels.

**WHAT IS SKIN CANCER?**

Skin cancer develops when something causes skin cells to grow irregularly. The most common risk factor is exposure to UV light, like sunlight or tanning beds.

People of all races and skin colors can develop skin cancer, but historically there has been more research and documentation of how it presents in people with lighter skin. People with darker skin are often diagnosed later than their lighter-skinned peers, putting them at higher risk of complications. Doctors and scientists are working to better document how skin cancer develops in people of color to mitigate this.
TYPES OF SKIN CANCER

- **Basal cell carcinoma** is the most common form of skin cancer. It develops in the basal cells, the cells that grow new skin cells.
- **Squamous cell carcinoma** is the second most common form of skin cancer. It develops in the squamous cells, which are the cells that make up the outer part of the epidermis.
- **Melanoma** is considered the most dangerous form of skin cancer because it is more likely than the others to spread to other parts of the body. It develops in the melanocytes, which are the cells that create melanin, the substance that gives skin its color.

Additional rare forms of skin cancer include Kaposi sarcoma, Merkel cell carcinoma, and sebaceous gland carcinoma.

This flyer will focus on the diagnosis and treatment of melanoma. If you would like to learn more about other types of skin cancer, please reference our flyer: Laboratory Tests related to Non-Melanoma Skin Cancer

There are four main subtypes of melanoma:

- **Superficial spreading melanoma** is the most common type of melanoma, accounting for about 70% of cases. It spreads outward on the skin’s surface, although it may also grow into deeper layers. It usually appears as a mole with an irregular border and can have various colors such as black, red, blue, brown, grey, or white.
- **Nodular melanoma** is the second most common type of melanoma, accounting for about 15-20% of cases. It is a raised growth that grows down into the skin. Some nodular melanomas are shaped like mushrooms and have a stem or stalk. They are usually black, but can also be red, pink, or skin colored.
- **Lentigo maligna melanoma** accounts for 10-15% of melanoma cases and develops from the skin condition called lentigo maligna. Lentigo maligna melanoma usually appears as a brown blotchy patch on the skin and spreads slowly. It occurs more often in older adults, and because of its appearance and slow spread, it is often confused with sun damage.
- **Acral lentiginous melanoma** accounts for 5% of melanoma cases and is more frequently found in people with darker skin tones. It usually looks like a small, flat, discolored patch or spot on the skin. Typically, it spreads outward before growing deeper into the skin. It commonly develops on the soles of the feet, the palms of the hands, or under the nails.

COMMON SIGNS AND SYMPTOMS OF MELANOMA

The first sign of skin cancer is usually a change in the skin’s texture or appearance. The most common sign of melanoma is a new pigmented spot on the skin that is changing in shape, size, or color. They will often look different than the moles or freckles around them.

Doctors recommend the ABCDE rule to monitor skin for potentially dangerous changes for moles:

- **A**symmetry: An irregularly shaped mole or growth.
- **B**order: A mole with blurry or irregularly shaped edges.
- **C**olor: A mole with more than one color.
- **D**iameter: A mole or growth larger than a pencil eraser (6 millimeters).
- **E**volution: Changes in shape, color, or size of a mole or growth.

Other signs of melanoma include a sore that doesn’t heal; redness or swelling beyond the mole; itchiness, tenderness, or pain; and oozing or scaliness on the surface of the mole.

Patients who observe any of these symptoms should talk to their primary care physician or a dermatologist. A dermatologist is a doctor that specializes in treating skin conditions and will closely check the patient’s skin for any irregularities or concerning growths.
LABORATORY TESTS RELATED TO DIAGNOSING MELANOMA

If a dermatologist finds a growth that may be cancerous, they will perform a biopsy. They will numb the area and then remove a skin sample. The sample will be sent to a lab, where a pathologist will look at it under a microscope. There are three types of biopsies that are used to diagnose skin cancer.

- **Punch Biopsy:** The doctor uses a tool called a biopsy punch to remove a small circular piece of skin.
- **Shave Biopsy:** The doctor uses a sharp blade to remove the top few layers of skin.
- **Excisional and Incisional Biopsies:** The doctor uses a scalpel to remove a tumor that has grown deeper in the skin. They usually remove the entire growth, which is called an excisional biopsy. In some cases, they may only remove part of the growth, which is an incisional biopsy.

Melanoma can spread quickly throughout the body and reach lymph nodes, the brain, or other organs before the skin lesion is identified. Rarely, the cancer will spread, and the skin lesion will go away without any treatment. If there is concern that the melanoma has spread, doctors will often perform a biopsy on lymph nodes or other areas of concern. These biopsies are often more intensive than the ones used to examine the skin. Types of biopsies that may be used include the following:

- **Fine Needle Aspiration:** The doctor inserts a very thin, hollow needle into the lymph node and collects a small amount of cells. If the lymph node is near the body’s surface, the doctor can aim the needle by feeling with their hands. If the lymph node is deeper in the body, they will use imaging like ultrasound or a CT scan to guide the needle. The samples removed during the biopsy will be sent to the lab and examined under a microscope by a pathologist to confirm if the cancer has spread.
- **Excisional Lymph Node Biopsy:** The doctor will remove the whole lymph node through a small cut in the skin. Depending on the location of the lymph node, the area will be numbed, or the patient will be sedated. These biopsies are performed if the doctor suspects the cancer has spread, but a fine needle aspiration wasn’t done or didn’t find any melanoma cells. The samples removed during the biopsy will be sent to the lab to be examined by a pathologist under the microscope to confirm if the melanoma has spread to the lymph node.
- **Sentinel Lymph Node Biopsy:** These biopsies are done on patients diagnosed with melanoma that is at risk of spreading. Doctors will inject the patient with small amounts of a radioactive substance and/or blue dye near the site of the skin lesion. They observe what lymph nodes collect the material first. These are called sentinel nodes, and they are where cancer would likely spread first. The sentinel nodes are removed and examined by a pathologist under the microscope. If there is no melanoma in these nodes, it is very unlikely that the cancer has spread elsewhere, and there is no additional surgery. If the pathologist sees signs of melanoma, the surgeon may remove the rest of the lymph nodes in the area for the pathologist to examine.

In some cases, a pathologist cannot determine the type of cancer just by looking at the biopsy under a microscope. In these cases, they will work with the lab to perform additional tests on the sample.

- **Immunohistochemistry (IHC):** This process uses tissue from patient samples prepared on glass slides and special antibodies to check for certain markers on the tumor cells called antigens. Different types of cancer have different antigens, so when the antibodies bind to specific antigens, they help the pathologist to tell the difference between melanoma and other types of cancer. The antibodies are attached to a chemical that displays a color (usually brown or red), which allows the pathologist to see if the test is positive under the microscope.
- **Fluorescence in situ hybridization (FISH):** This test identifies genetic changes in DNA, like chromosomal abnormalities that create specific proteins that cause cancer cells to grow and reproduce faster. FISH is used both to identify cancer types and to guide treatment options. During a FISH test, small stretches of DNA called DNA probes attach to matching stretches in the tumor cells. The DNA probes are marked with a dye that responds to fluorescent light. When the sample is put under a fluorescent light microscope, they highlight gene changes in the tumor DNA. FISH is usually performed on tissue on a glass slide or on tumor cells in a Petri dish that have been removed and allowed to multiply in the laboratory.
- **Comparative genomic hybridization (CGH):** This test compares the DNA in two samples to identify changes in the DNA. Pathologists will use it to compare the DNA of tumor tissue to the DNA of healthy tissue. By examining the differences in the DNA, the pathologist can better determine if the tissue is cancer, and if it is, what type.
- **Gene expression profiling (GEP):** Gene expression is the process where information is taken from genes and used to make proteins within cells. DNA transcription creates a substance called messenger RNA. A process called RNA transcription uses messenger RNA to create proteins. At any given time, only some of a cell’s genes are making RNA. Gene expression profiling identifies what genes are “turned on” and creating messenger RNA. This information can be used to help diagnose cancer and guide cancer treatments.
After examining the biopsies, the pathologist will stage the melanoma. Staging identifies how much cancer is in the body and how much it has spread.

**MELANOMA STAGING**

**Stage 0 (also called melanoma in situ):** The tumor is only in the top layer of skin.

**Stage I:** The tumor is less than 2 mm thick, and there’s no evidence that it has spread.

**Stage II:** The tumor is between 1 and 4 mm thick, and there’s no evidence it has spread.

**Stage III:** The melanoma has spread to nearby lymph nodes or nearby skin.

**Stage IV:** The melanoma has spread to distant lymph nodes or organs like the lungs, liver, or brain.

**LABORATORY TESTS RELATED TO TREATING AND MANAGING MELANOMA**

**BRAF Genetic Test:** This test identifies if a tumor has a mutation in the BRAF gene. The BRAF gene is responsible for creating BRAF proteins. The BRAF protein is responsible for managing how and when cells grow. If the gene is mutated, cancer will grow larger more quickly. If the tumor is BRAF positive, doctors will have a better sense of how the tumor will respond to treatment, how the tumor will grow, and what medicines could be more effective to target the cancer cells.

**UNDER THE MICROSCOPE**

In this picture, the malignant melanoma cells are present in nests in the epidermis (blue arrow) and the dermis (yellow arrow). The melanoma cells have dark nuclei (hyperchromasia) and vary in size and shape (pleomorphism). There is light brown pigment (melanin) in the cytoplasm of some of these cells.

**QUESTIONS TO ASK YOUR DOCTOR**

- What subtype of melanoma do I have?
- Is my melanoma invasive?
- Are cancer cells present anywhere else in my body?
- What tests do I need before we can decide on treatment?
- Does my melanoma have any known genetic mutations?
- Why do you suggest this treatment?
- What are the long-term effects of this treatment?
- Are my family members at higher risk of developing melanoma?
- What support services are available to me and my family?
“Without the lab, I wouldn’t likely be alive. The first immunotherapy treatment I was on nearly killed me, so clearly it was halted. The tumors in my mediastinum were actively growing - causing a restriction in my airway. Without the BRAF mutation test that made that type of immunotherapy an option, I may have gone into the hospital to be intubated and not come out.”

In 2011, at the age of 30, Jim had a suspicious mole removed from the skin over his lower right jaw. The removed tissue was sent to a lab, where a pathologist determined it was melanoma. After his diagnosis, his doctors checked his lymph nodes to see if his cancer had spread, and since there was no sign of cancer, they told him he was in the clear.

Five years later, Jim started to have unexplained symptoms: his calves and feet were swollen, he was exhausted, and he was having severe chest pain. His symptoms escalated, he started to experience extreme dizziness and had to go to the hospital. At the hospital, an MRI revealed that he had a cerebellar mass and tumors in his lung and mediastinum, which is the middle part of the chest cavity where the heart, lymph nodes, major blood vessels and airways are located. After examination, his doctors told him that his melanoma had spread, or metastasized.

After some trial and error, Jim’s tumor was tested for a BRAF mutation. The test was positive, which made him a candidate for a new treatment option. The treatment was successful, and Jim’s cancer is now in remission.